Plasma Cholecystokinin Response to a Liquid Fat Meal in Vagotomized Patients

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Since previous studies have suggested that in patients with truncal vagotomy (TV) the plasma cholecystokinin (CCK) secretion in response to nutrients is impaired, we have measured the plasma CCK response to a liquid fat meal (250 ml 20% Intralipid) in six patients with TV and pyloroplasty. We have compared the results with those obtained in eight normal subjects, six patients with duodenal ulcer, and eight patients with highly selective vagotomy (HSV). Plasma CCK concentrations were measured by a sensitive and specific radioimmunoassay employing antibody T204 directed against the sulphated tyrosine region of CCK. Basal plasma CCK concentrations were not significantly different among the four groups studied (2.1 ± 0.4 pmol/l in normal subjects, 2.8 ± 0.5 pmol/l in duodenal ulcer patients, 3.1 ± 0.5 pmol/l in patients with TV, and 2.7 ± 0.5 pmol/l in patients with HSV). The increments in plasma CCK after ingestion of the fat meal in patients with TV (15.7 ± 3.1 pmol/l) and HSV (14.9 ± 1.6 pmol/l) were significantly higher ($p < 0.01$) than those in normal subjects (4.8 ± 0.9 pmol/l) and in patients with duodenal ulcer (5.5 ± 0.6 pmol/l). Similarly, the integrated plasma CCK secretions in patients with TV (554 ± 139 pmol/l, 120 min) and in patients with HSV (876 ± 132 pmol/l, 120 min) were significantly increased ($p < 0.05$) compared to those in normal subjects (187 ± 29 pmol/l, 120 min) and in patients with duodenal ulcer (264 ± 35 pmol/l, 120 min). It is concluded that patients with TV and HSV show an increased plasma CCK secretion in response to a liquid test meal.

PREVIOUS STUDIES have shown that in patients with truncal vagotomy (TV) the pancreatic enzyme secretion in response to nutrients is impaired.[1-3] Since the pancreatic enzyme response to exogenous hormonal stimulants was not impaired, it was postulated that vagotomy reduced the amount of cholecystokinin (CCK) released from the small intestinal mucosa in response to feeding.[1-5] In the absence of reliable radioimmunoassays for CCK in plasma, this suggestion could neither be confirmed nor rejected.

Supported by the Netherlands Foundation for Medical Research FUNGO (grant no. 13-37-32).

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Submitted for publication: March 19, 1984.

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We have recently developed a specific radioimmunoassay for CCK sufficiently sensitive to measure the low plasma CCK concentrations in human plasma.[6,7] Using this radioimmunoassay, we have measured the plasma CCK response to a liquid fat meal in patients with TV, and we have compared the results with those obtained in normal subjects, in patients with duodenal ulcer, and in patients with highly selective vagotomy (HSV).

Patients and Methods

Six patients with TV and pyloroplasty (five male, one female, mean age 49 years, range 27–65 years), eight patients with HSV (seven male, one female, mean age 36 years, range 26–51 years), six patients with duodenal ulcer (four male, two female, mean age 44 years, range 23–70 years), and eight normal subjects (seven male, one female, mean age 33 years, range 21–60 years) were studied.

After an overnight fast, the subjects ingested a liquid test meal (250 ml 20% Intralipid, Kabi Vitrum, Stockholm, Sweden) within 10 minutes. Plasma samples for CCK were obtained at −5, 0, 10, 20, 30, 40, 50, 60, 75, 90, 105, and 120 minutes. Plasma CCK concentrations were measured by a sensitive and specific radioimmunoassay.[6,7] The antibody used (T204) bound to all CCK-peptides containing both the sulphated tyrosine region and the carboxyl-terminus of CCK (Fig. 1). The antibody did not significantly bind to synthetic amino-terminal CCK-peptides (CCK 1-15, CCK 1-21), mid-fragments (CCK 10-20, CCK 16-27), or carboxyl-terminal CCK-peptides devoid of the sulphated tyrosine region (unsulphated CCK 8, CCK 4). The antibody did not bind to unsulphated gastrin 17 and gastrin 34, while the cross-reactivity with sulphated gastrins was negligible (approximately two per cent). Furthermore, there was no binding

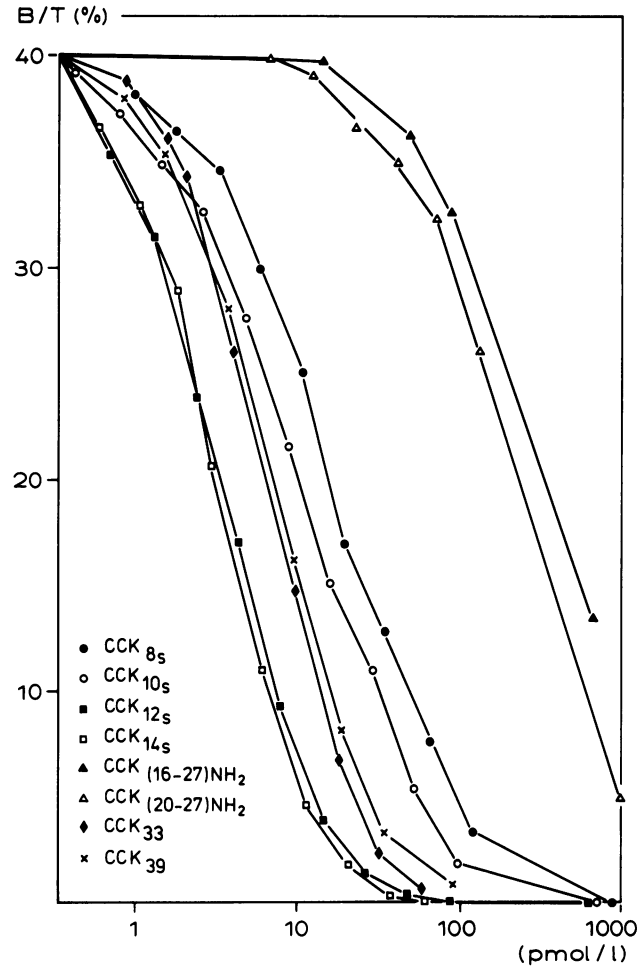

FIG. 1. Binding of CCK-peptides to antibody T204 using CCK 33 coupled to ^{125}I-hydroxyphenylpropionic acid succinimide ester (Bolton Hunter reagent) as label.

to structurally unrelated regulatory peptides including insulin, glucagon, somatostatin, pancreatic polypeptide, secretin, gastric inhibitory polypeptide, vasoactive intestinal polypeptide, bombesin, gastrin-releasing peptide, and neurotensin. 99% pure porcine CCK 33 (V. Mutt, Karolinska Institute, Stockholm, Sweden) coupled to ^{125}I-hydroxyphenyl-propionic acid-succinimide ester (Bolton-Hunter reagent, New England Nuclear, Boston, MA) was used as label and 99% pure porcine CCK was used as standard preparation. The concentration of CCK 33 displacing 50% of the label from the antibody (inhibition dose 50, ID 50) was 3.3 pmol/l incubation mixture. Plasma samples were extracted using 96% ethanol. A nonequilibrium system was used with 72 hours preincubation followed by 24 hours incubation after addition of the labeled peptide. The detection limit of the assay was between 0.5 and 1.0 pmol/l plasma. Using this assay, it was shown that CCK in plasma is heterogeneous and that antibody T204 recognizes all molecular forms of CCK detected by a carboxyl-terminal CCK/gastrin antibody.[7] The intra-assay variation was 11.5% at 1.2 pmol/l, 8.4% at 2.5 pmol/l, and 4.6% at 8.0 pmol/l (N = 5). The interassay variation was 26.1% at 1.3 pmol/l, 11.3% at 2.6 pmol/l, and 15.4% at 8.8 pmol/l (N = 5).

Results were expressed as the mean ± 1 SEM. Integrated CCK secretion was determined by calculating the area under the curve after subtraction of the basal value. Statistical analysis was done by Student's t-test for paired and unpaired results. Informed consent was obtained from all subjects studied.

Results

Basal plasma CCK concentrations were not significantly different in the four groups of subjects studied (2.1 ± 0.4 pmol/l in normal subjects, 2.8 ± 0.5 pmol/l in patients with duodenal ulcer, 3.1 ± 0.5 pmol/l in patients with TV, and 2.7 ± 0.5 pmol/l in patients with HSV). Ingestion of 250 ml 20% Intralipid induced increases in plasma CCK in all subjects studied (Figs. 2 and 3). In normal subjects plasma CCK concentrations at 10, 20, 30, 40, 50, 60, 75, and 90 minutes were significantly increased over basal ($p < 0.05$–$p < 0.0005$); in duodenal ulcer patients all postprandial CCK concentrations were significantly higher than basal value ($p < 0.05$–$p < 0.001$); in patients with TV and pyloroplasty plasma CCK levels at 20, 30, 40, and 60 minutes were

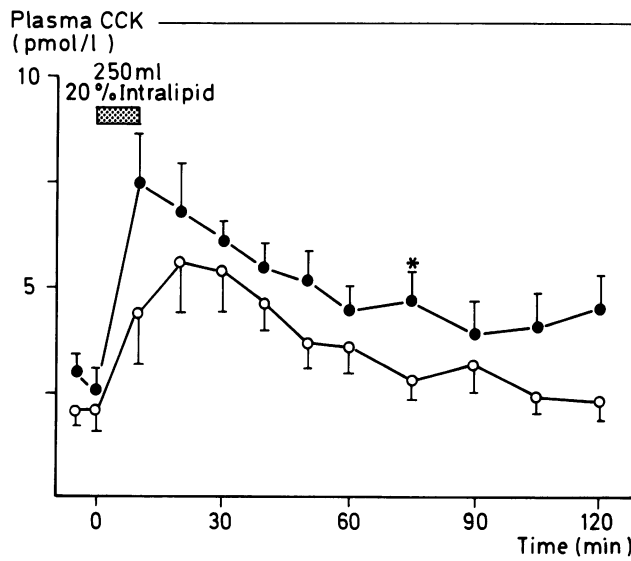

FIG. 2. Plasma CCK concentrations in response to a liquid fat meal (250 ml 20% Intralipid) in six patients with duodenal ulcer (closed circles) and in eight normal subjects (open circles). The asterisk denotes a significant difference from the normal subjects ($p < 0.05$).

significantly increased over basal value ($p < 0.05$–$p < 0.005$); and in patients with HSV plasma CCK concentrations at 10, 20, 30, 40, 50, 60, 75, 90, and 105 minutes were significantly higher than basal value ($p < 0.05$–$p < 0.0005$). Apart from the CCK concentration at 75 minutes ($p < 0.05$), plasma CCK concentrations in normal subjects and patients with duodenal ulcer were not significantly different (Fig. 2).

As shown in Figure 3, in patients with TV, plasma CCK concentrations at 20, 30, and 40 minutes and in patients with HSV, those obtained at 10, 20, 30, 40, 50, 60, 75, and 105 minutes were significantly elevated over the concentrations in the normal subjects ($p < 0.05$–$p < 0.0005$). Apart from the concentration at 60 minutes ($p = 0.04$), plasma CCK concentrations in patients with TV and HSV were not significantly different. The increments in plasma CCK in patients with TV (15.7 ± 3.1 pmol/l) and in patients with HSV (14.9 ± 1.6 pmol/l) were significantly higher than those in normal subjects (4.8 ± 0.9 pmol/l; $p < 0.005$ and $p = 0.0001$) and in patients with duodenal ulcer (5.5 ± 0.6 pmol/l; $p < 0.01$ and $p = 0.0005$). The increments in both groups of vagotomized patients were not significantly different from each other. Also, the increments in plasma CCK in patients with duodenal ulcer and normal subjects did not significantly differ.

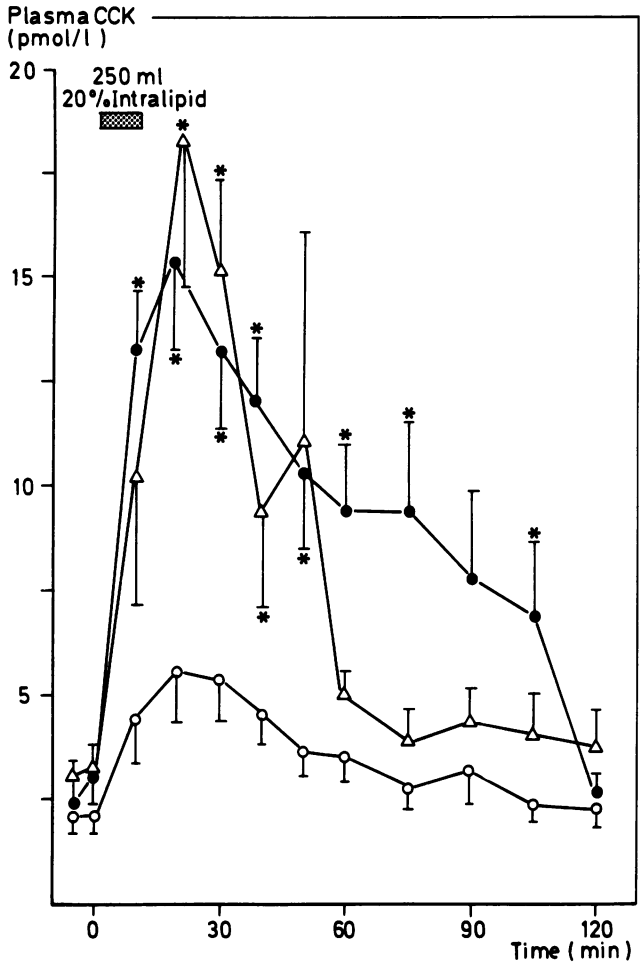

FIG. 3. Plasma CCK concentrations in response to a liquid fat meal (250 ml 20% Intralipid) in six patients with truncal vagotomy and pyloroplasty (triangles), in eight patients with highly selective vagotomy (closed circles), and in eight normal subjects (open circles). Asterisks denote significant differences from the normal subjects ($p < 0.05$–$p < 0.0005$).

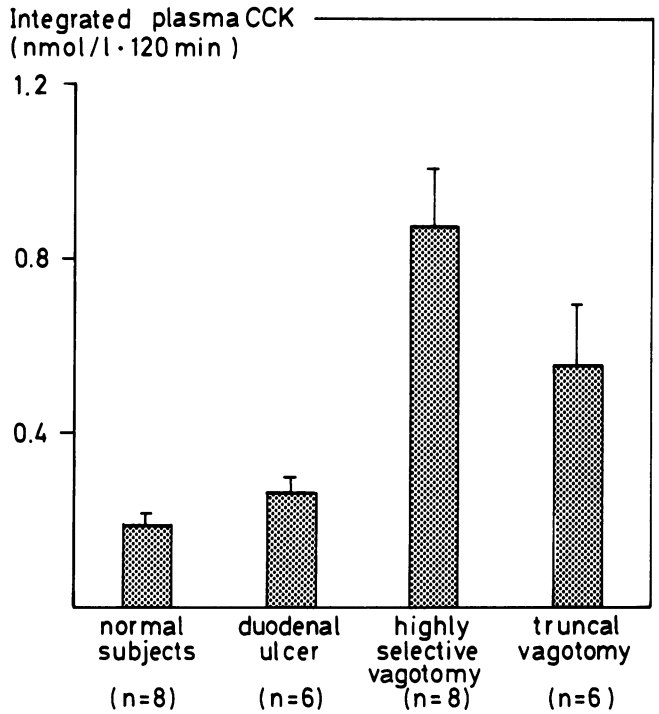

FIG. 4. Integrated plasma CCK secretion in response to a liquid fat meal (250 ml 20% Intralipid) over 2 hours in eight normal subjects, in six patients with duodenal ulcer, in eight patients with highly selective vagotomy, and in six patients with truncal vagotomy.

The integrated plasma CCK secretions over 120 minutes in patients with TV (554 ± 139 pmol/l, 120 min) and HSV (876 ± 132 pmol/l, 120 min) were significantly increased over that in normal subjects (187 ± 29 pmol/l, 120 min; $p = 0.01$ and $p < 0.0005$, respectively), whereas the integrated plasma CCK secretion in patients with duodenal ulcer (264 ± 34 pmol/l, 120 min) did not significantly differ from that in the normal subjects (Fig. 4). The integrated plasma CCK secretion in both groups of vagotomized patients did not significantly differ from each other. As shown in Figure 5, the differences between the groups over 2 hours were almost exclusively due to differences in the first hour after ingestion of the meal. The integrated plasma CCK secretions over 60 minutes in patients with TV (492

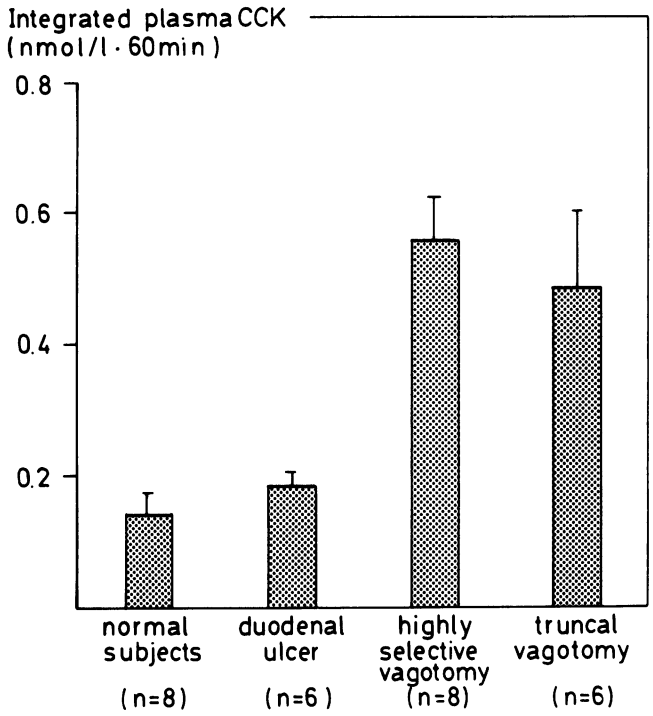

FIG. 5. Integrated plasma CCK secretion in response to a liquid fat meal (250 ml 20% Intralipid) in the first hour after ingestion in eight normal subjects, in six patients with duodenal ulcer, in eight patients with highly selective vagotomy, and in six patients with truncal vagotomy.

± 118 pmol/l, 60 min) and HSV (560 ± 60 pmol/l, 60 min) were significantly increased over that in the normal subjects (140 ± 22 pmol/l, 60 min; $p = 0.005$ and $p < 0.0001$, respectively). Again, there was no statistically significant difference between patients with TV and HSV. Furthermore, the integrated plasma CCK secretion in patients with duodenal ulcer (185 ± 23 pmol/l, 60 min) did not significantly differ from that in the normal subjects.

Discussion

In the absence of reliable radioimmunoassays for CCK, pancreatic enzyme secretion was used as a bioassay system to monitor CCK secretion from the upper small intestine.[8] Using this bioassay system, it was shown that in patients with TV, pancreatic enzyme secretion during perfusion of the small intestine with amino acids was impaired.[1,2] An impaired pancreatic enzyme secretion in patients with TV was also observed after ingestion of a liquid test meal[3] and in vagotomized dogs after various intestinal stimuli.[4,5,9] Since the pancreas responded normally to exogenous hormonal stimulation, it was suggested that, after TV, the CCK secretion in response to nutrients was reduced.[1-4] However, in later studies in dogs with a transplanted pancreas, it was indirectly shown that vagotomy did not affect CCK secretion in response to nutrients.[10] In a recent study, using a radioimmunoassay for large molecular forms of CCK, Fried and co-workers found that TV did not reduce CCK secretion in response to intraduodenal oleate in dogs.[9]

In the current study, we have measured plasma CCK responses to a liquid fat meal in patients with TV and we have compared the results with those obtained in normal subjects, in patients with duodenal ulcer, and in patients with HSV. Plasma CCK was measured by a sensitive and specific radioimmunoassay.[6,7] The antibody used bound to all CCK-peptides containing the sulphated tyrosine region and the carboxyl-terminus of CCK. Since both the sulphated tyrosine region and the carboxyl-terminus are required for biological activity of CCK, it can be concluded that the current assay measures biologically active forms of CCK. Using this assay, we found that, both in patients with TV and in patients with HSV, the CCK response to the liquid fat meal was increased compared to that in normal subjects and in patients with duodenal ulcer. Since all patients had undergone vagotomy because of duodenal ulcer disease, these results suggest that vagotomy results in an increase in the plasma CCK response to a liquid fat meal. The mechanism for this increased plasma CCK secretion in vagotomized patients is unknown, but is probably related to rapid gastric emptying in such patients. It has repeatedly been shown that, both in patients with TV and in patients with HSV, the initial gastric emptying of liquid meals is increased.[3,11-14] As shown in Figures 4 and 5, the differences in integrated plasma CCK secretion over 2 hours between vagotomized patients and nonoperated subjects were almost exclusively due to differences found in the first hour after ingestion of the meal. Furthermore, it has recently been reported that in patients with partial gastrectomy, another condition characterized by rapid gastric emptying, the plasma CCK secretion after a liquid fat meal is also increased.[15] This increased CCK secretion in gastrectomized patients was independent of the type of anastomosis between the gastric remnant and the small intestine.[15]

In conclusion, patients with either TV or HSV show an increased CCK secretion in response to a liquid fat meal, whereas the CCK secretion in patients with duodenal ulcer is similar to that in normal subjects. Therefore, vagotomy does not impair the plasma CCK secretion in response to nutrients.

Acknowledgments

The authors are indebted to Professor N. Yanaihara for the generous gift of synthetic CCK-peptides and to Dinie Graven for secretarial assistance.

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